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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,235	08/27/2001	Girish Sahni	07064-009002	5356

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/940,235	SAHNI ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 32* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0104*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Express Abandonment, Request for Continuing Examination, and Amendment of February 11, 2003 are acknowledged. It is acknowledged that applicants have cancelled Claim 2 and amended Claims 1, 3, and 32. Claims 1, 3, and 32 are pending and are hereby reexamined.

Specification Objections

The specification is objected to for lack of clarity on page 55, parg 2, line 7- page 56, parg 1, line 5. Said lines state that "removal of trace amounts of plasmin...led to very high periods of lag" and that "addition of small quantities of preformed human plasmin ...enhanced the lag periods". Taken together these phrases are unclear. Based on Applicant's response of February 11, 2003, page 14, parg 2, it is believed that the specification is meant to state that upon removal of plasmin, the lag increased, while upon addition of plasmin, the lag decreased. Clarification is required.

Claim Objections

Claim 3 is objected to for the phrase "time lag is ranging between", which would be more clearly stated as "time lag ranges between". Correction is requested.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For Claim 1 the phrase "functional component" on lines 2-3 and 5 is unclear. It is unclear what function said component has; furthermore, if the "component" is a structural fragment, "fragment or domain" are clearer. For purposes of examination, it assumed that said phrase is meant to recite a catalytically active fragment. Correction is required.

For Claim 1, the use of the phrase "whereby" on line 4 is unclear.

For Claim 1, the phrase "retaining up to 100% plasminogen activity" is unclear, as the recited protein has plasminogen activator activity, not plasminogen activity.

For Claim 1, the phrase "desired time-lag" is indefinite without disclosure of what is desired.

For Claim 1, recitation of "residues 16-383" without identification of a sequence is indefinite. Correction is required.

For Claim 1, line 3, the phrase "containing essentially" is unclear; it is unclear whether said phrase is meant to recite "comprising" or "consisting essentially of". Clarification is required.

For Claim 1, lines 4-5, the phrase "finger-type fibrin binding domain pairs of 1-2 and/or 4-5" is unclear. Correction is required. For purposes of examination, it assumed that said phrase is meant to recite "fibronectin binding domains pairs of domains 1 and 2 and/or domains 4 and 5 of fibronectin".

Claims 3 and 32, as dependent from Claim 1, are rejected under 35 U.S.C. 112, second paragraph, for the same reasons.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, and 32 are rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for the hybrid plasminogen activators, comprising fusion of streptokinase with fibrin binding-domain proteins, as encoded by the sequences set forth in Figs 17b, 19b, 21b, and 22b. However, the specification does not reasonably provide enablement for any hybrid plasminogen activator comprising any streptokinase, or any fragment thereof consisting essentially of residues 16-383, and any pair of fibrin binding-domains derived from fibronectin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1 and 32 are so broad as to encompass any hybrid plasminogen activator comprising any streptokinase, or functional fragment thereof containing essentially residues 16-383, and any pair of fibrin binding-domains, 4 and 5 and/or 1 and 2, derived from fibronectin wherein, plasminogen activation occurs after a time-lag. Claim 3 is so broad as to encompass any plasminogen activator of Claim 1, wherein the time-lag ranges between 5 to 30 minutes. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of plasminogen activators broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired plasminogen activation and fibrin binding requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification),

and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the plasminogen activators encoded by the sequences set forth in Figs 17b, 19b, 21b, and 22b.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 1 and 3, which encompasses any hybrid plasminogen activator comprising any streptokinase, or functional fragment thereof containing essentially residues 16-383, and any pair of fibrin binding-domains, 4 and 5 and/or 1 and 2, derived from fibronectin wherein, plasminogen activation occurs after a time-lag. The specification does not support the broad scope of Claim 3, which encompasses any plasminogen activator of Claim 1, wherein the time-lag ranges between of 5 to 30 minutes. The specification does not support the broad scope of Claims 1, 3 or 32 because the specification does not establish: (A) the sequences of the streptokinases and FBDs that can be used to make hybrid plasminogen activators having the desired characteristics; (B) regions of any activator's structure which may be modified without effecting the plasminogen activation or fibrin binding; (C) the general tolerance of the plasminogen activation and fibrin binding to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any residues with

an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of hybrid plasminogen activators. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that said rejection under 35 U.S.C. 112, first paragraph, for lack of enablement, be withdrawn, Applicants provide the following arguments. The rejection is requiring that the specification provide detailed teachings of essentially **every single possible species**. The rejection, characterizing the invention as covering "any modified hybrid plasminogen activator comprising any modified streptokinase and any pair of modified fibrin binding domains ignores the claim language, which specify that the activator exhibits a **plasmin-dependent activation mechanism that delays plasminogen activation**. The claims also specify that the activator **must include residues 16-383 of human streptokinase**. [All Applicant's emphasis.] The specification disclosed the specific molecular designs that confer the time-lag activation. It simply is inaccurate to say that the specification provides no guidance as to the parent sequence to be modified. The claims are quite specific about the parent SK

sequences and the FBD sequences to be modified. Moreover, human SK is well characterized and modification of residues with an expectation of obtaining the desired biological function is clear. The ability to screen for FBDs that cause a lag but are cleaved by fibrin to yield active SK is similarly clear.

These arguments are not found to be persuasive for the following reasons. The rejection is not requiring that the specification provide detailed teachings of essentially every single possible species, but is requiring that a person of ordinary skill in the art be able to make and use the full scope of the claimed invention. Enablement can be provided by examples and/or guidance on how to make the structure of the recited proteins and how those proteins can be used i.e. their function. The specification adequately enables a skilled artisan to use the recited invention, but does not enable the skilled artisan to make the recited invention, as the structure of the full scope of proteins encompassed by the invention is not taught by either example or guidance. It is acknowledged that the present claims limit the scope of the invention to activators exhibiting plasmin-dependent activation mechanism that delays plasminogen activation. However, said limitation only provides further guidance as to how to use the recited invention, not how to make it. The claims do not recite that the activator must include residues 16-383 of human streptokinase and, as described above, recitation of said residue without reference to a specific sequence is indefinite. Furthermore, the specification discloses the use of *S. equisimilis* strain H46A streptokinase for preparation of the recited constructs (pg 28, line 1), not the human enzyme. It is acknowledged that the specification provides guidance that fusion of FBDs to both the N- and C-termini causes a greater lag in activation of plasminogen, than fusion of FBDs to either the N- or C-terminus alone (pg 58, parg 2-pg 59, parg 1). However,

said guidance is insufficient to teach one of skill in the art how to make the full scope of the recited invention. The claims do not recite a parent sequence for either streptokinase or the FBDs and the neither the claims nor the specification disclose how any parent sequences may be modified and still obtain the required function. It is acknowledged that the specification teaches how to test for a lag in activation of plasminogen by any streptokinase/FBDs fusion protein. However, the number of proteins to be screened to enable one of skill in the art to distinguish those proteins with the desired biological characteristics represents undue experimentation.

Therefore, Claims 1, 3, and 32 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

Claims 1, 3, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of hybrid plasminogen activator proteins. The specification teaches the structure of only four representative species of such proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a hybrid plasminogen activator having a plasmin-dependent activation mechanism that delays plasminogen activation. Given this lack of structural description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the full scope of the claimed invention.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. The claims now specify the parent sequences for both components of the hybrid activator, which overcomes the rejection based on lack of structure in the claims. This argument is not found to be persuasive because, as described above for lack of enablement on how to make the claimed invention, the claims do not specify either the parent sequences or how any parent sequences can be modified and still obtained the desired function.

Claim Rejections - 35 USC § 103

Rejection of Claims 1, 3, and 32 under 35 U.S.C. 103(a) as being unpatentable over Brown et al, 1992 in view of Malke, 1990 (IDS) and further in view of Atkinson et al, 1998 is withdrawn. In support of their request that said rejection be withdrawn, Applicants provide the following critical argument.

The initial time-lag observed in the invention is actually due to a plasmin-dependent mechanism operative in these new forms. The plasmin-dependence of PG activation by the hybrids disclosed in the application is established in Example 8, paragraph 2, showing that, upon removal of plasmin, the lag increased, while upon addition of plasmin, the lag decreased. Further, the activation of PG by the hybrids, and concomitant abolishment of the lag, was found to coincide with the cleavage of the fused fibrin binding domains from the SK portion of the hybrid (Example 8). Unlike native SK, which forms an activator enzyme with the zymogen (PG) almost instantaneously, the new forms require the presence of plasmin to activate substrate. Since free plasmin is absent in the circulation normally, but present in the blood clots, the activators with such a property, together with strong fibrin affinity, are indisputably improved in terms of their therapeutic properties related to improved localized activation. The presence of

these two properties simultaneously in our constructs, and the unique mechanism associated with these, is clearly distinct both from Malke et al's and Brown et al's constructs.

Since the pathological "target" clot is relatively plasmin-rich, it would allow the in situ activation of the modified SK molecules onces they home into the clot by virtue of their fibrin affinity. *More importantly, since free plasmin is rare or absent in circulation, the constructs would remain in an inactive state while sojourning the circulating system until their absorption to the clot.*

The examiner is not free to ignore the assertion and documentation of a surprising result. In re Soni, 54 F.3d 746, 34 USPQZd 1684 (Fed. Cir. 1995). No where does the Examiner provide an analysis of this issue.

These arguments are found to be persuasive. The requirement for plasmin for the SK-fusion proteins to activate PG is an unexpected, non-obvious result. None of Brown et al, Malke, or Atkinson et al, suggest making a fusion protein, comprising SK and fibrin binding domains, that would have the functional characteristics of delayed PG activation due to a dependence on plasmin. Therefore, rejection of Claims 1, 3, and 32 under 35 U.S.C. 103(a) as being unpatentable over Brown et al, 1992 in view of Malke, 1990 (IDS) and further in view of Atkinson et al, 1998 is withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
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